

**METHOD OF HYDROBORATING ALCOHOLS AND
REDUCING FUNCTIONAL GROUPS USING A
RECYCLABLE FLUOROUS BORANE-SULFIDE**

STATEMENT OF GOVERNMENTAL INTEREST

5 This invention was made with government
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CROSS REFERENCE TO RELATED APPLICATION

10 This application claims the benefit of
U.S. provisional patent application Serial No.
60/398,414, filed July 25, 2002.

FIELD OF THE INVENTION

15 The present invention relates to fluororous
borane-sulfides and to facile and environmentally
acceptable methods of hydroborating alkenes and
alkynes and of reducing various organic functional
groups. More particularly, the present invention
relates to the hydroboration of alkenes and alkynes
and to the reduction of functional groups using a
20 recyclable, fluororous borane-sulfide.

BACKGROUND OF THE INVENTION

25 Borane is one of the most useful and
widely used organic reagents. Borane enables the
hydroboration of alkenes and alkynes, and a myriad
of chemical transformations arising from the so-
formed organoborane derivatives. Borane also en-
ables reductions of a host of other organic func-

tionalities. The instability and low reactivity of diborane toward alkenes has resulted in the development of numerous more reactive borane complexes. In addition, the pyrophoric nature of borane renders both its use and transportation hazardous. Therefore, borane typically is coordinated, e.g., to tetrahydrofuran ($\text{BH}_3 \cdot \text{THF}$)^{1,2} or dimethyl sulfide ($\text{BH}_3 \cdot \text{SMe}_2$, i.e., BMS)³⁻⁶, with BMS being preferred because of its greater stability.

The hydroboration of alkenes and the reduction of numerous organic functional groups by borane-dimethyl sulfide (BMS) are extremely common transformations in organic synthesis.²⁻⁴ This includes the use of BMS as a relatively stable borane carrier for the generation of chiral boranes, such as diisopinocampheylborane, β -isopinocampheyl-9-borabicyclo[3.3.1]nonane, and other such chiral boranes.⁵ It also includes the use of BMS to generate the active species from chiral oxaborolidine precatalysts for use in asymmetric reductions.²⁹ BMS, therefore, is extremely widely used in academic and industrial laboratories, but much less so in industrial processes.

Although BMS is considerably more practical to use than borane itself, BMS suffers from the disadvantage of liberating stoichiometric amounts of dimethyl sulfide in the course of its reactions. Dimethyl sulfide is an extremely volatile (b.p. 37°C) and foul-smelling compound. The generation of dimethyl sulfide also is environmentally unacceptable, which makes BMS-mediated

reactions undesirable for large commercial applications. For example, if used in a large reaction scale, a BMS mediated reaction would require scrubbing of the waste stream. BMS also has stability
5 problems and is pyrophoric.

These disadvantages enormously restrict the use of BMS on an industrial scale. Attempts to overcome these problems include the use of water-soluble sulfides and nonvolatile sulfides,^{8,9} but
10 these approaches are deficient in terms of recyclability of the sulfide. Also, see H.C. Brown et al., *J. Org. Chem.*, 51, pp. 4970-4976 (1992).

For example, the disadvantages of BMS prompted investigators to use 1,4-thioxane⁷ as a less
15 volatile carrier for borane, and, more recently, bis(hydroxyethyl) sulfide,⁸ which has the additional advantage of being water soluble, and therefore is conveniently removed by aqueous extraction following reductions using $\text{BH}_3 \cdot \text{S}(\text{CH}_2\text{CH}_2\text{OH})_2$. Other sulfides
20 that have been used as carriers for borane include 1,2-bis(tert-butylthio)ethane and 1,4-bis(benzylthio)butane.⁹

The present invention, therefore, is directed to improved methods of hydroborating alkenes
25 and alkynes and of reducing various organic functionalities using borane in a large scale, and that overcome the disadvantages associated with prior synthetic methods using a borane-sulfide complex. The present invention particularly is directed to
30 using 2-(perfluorooctyl)ethyl methyl sulfide and similar fluororous sulfides as readily prepared, odor-

less, nonflammable sulfides for complexation and stabilization of borane. The fluorinated sulfides also are readily recycled.

SUMMARY OF THE INVENTION

5 The commercial, environmentally friendly hydroboration of alkenes and alkynes, and the reduction of various organic functional groups using borane, have been hindered because of the disadvantages and problems associated with using uncomplexed
10 borane or the generation of noxious by-products from borane complexes, such as dimethyl sulfide from BMS. Therefore, the present invention is directed to commercial scale methods of hydroborating alkenes and alkynes, and of reducing organic functionalities,
15 using a borane complex that overcomes the environmental and disposal problems associated with prior borane-mediated methods.

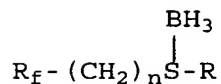
 In particular, the present invention is directed to a methods of hydroborating alkenes and
20 alkynes, and of reducing other organic functionalities, using a fluorous borane-sulfide to overcome problems associated with BMS and other sulfide-complexed boranes used in prior methods.

 As demonstrated hereafter, the present
25 invention enables all current applications of BMS to be conducted in a facile, safe, odorless manner. Thus, a mixture of a fluorous sulfide and a fluorous borane-sulfide, either as a solid, a suspension in a fluorinated solvent, or a solution in a suitable
30 organic solvent, such as dichloromethane, THF, or

benzotrifluoride, are direct replacements for BMS, but with greatly reduced environmental and toxicological hazards and odor. The present invention also has significant environmental and economic advantages because the spent fluorous borane-sulfide, enriched in the fluorous sulfide, can be recycled by contact with borane gas. Therefore, the discharge of sulfides, either water soluble or water insoluble, to the environment is minimized.

The improved hydroboration reaction is important because of the wide scope of the reaction with respect to preparing alcohols and other organic compounds, and its potential use on an industrial scale. An important feature of the present invention is to provide an improved hydroboration reaction that avoids the generation of environmentally unfriendly dimethyl sulfide, while maintaining the ease and broad scope of BMS reactions. An additional advantage would be use of a borane complex that can be quickly regenerated and recycled into the hydroboration or other reduction reactions.

Accordingly, the present invention is directed to a modified hydroboration reaction wherein a fluorous borane-sulfide complex is substituted for the BMS complex. In particular, one aspect of the present invention is to provide a fluorous borane-sulfide that overcomes the disadvantages associated with BMS and other complexing agents for borane. The fluorous borane-sulfide has a general structural formula (I)



(I)

wherein R_f is a fluorinated hydrocarbon chain containing one to twelve carbon atoms; R is
5 C_{1-4} alkyl or $(\text{CH}_2)_n - \text{R}_f$; and n is an integer 1 to 3.

Another aspect of the present invention is to provide a fluoros borane-sulfide of structural formula (I) wherein R_f contains four to ten carbon atoms and, preferably, is perfluorinated; R is
10 C_{1-4} alkyl, preferably, methyl or ethyl; and n is 2.

Another aspect of the present invention is to provide a fluoros borane-sulfide that avoids the stoichiometric generation of environmentally unfriendly dimethyl sulfide, incorporates a single,
15 relatively short perfluoroalkyl chain (e.g., four to eight carbon atoms), is soluble or dispersible in organic and fluorinated solvents, and is economical and easy to synthesize.

Yet another aspect of the present invention is to provide a method of hydroborating an
20 alkene or an alkyne, and a method of reducing organic functionalities, like ketones, nitriles, amides, and esters, using a fluoros borane-sulfide of structural formula (I).

25 Still another aspect of the present invention is to provide a method of regenerating and recycling the fluoros borane-sulfide of structural formula (I) by borating a fluoros sulfide of structural formula $\text{R}_f - (\text{CH}_2)_n - \text{S} - \text{R}$ generated in the hydro-

boration reaction to regenerate the fluororous borane-sulfide of structural formula (I).

Another aspect of the present invention is to provide a facile preparation of a viscous, odor-free fluororous sulfide, e.g., 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl methyl sulfide, its complex with borane, i.e., fluororous BMS, and its higher and lower homologs. In another aspect, the invention further provides the use of a fluororous borane-sulfide of structural formula (I) in hydroboration reactions and in the reduction of numerous other organic functional groups, and its regeneration and recycling.

These and other novel aspects and advantages of the present invention will become apparent from the following detailed description of the preferred embodiments.

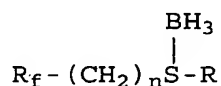
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is directed to improved methods for the facile commercial hydroboration of alkenes and alkynes, and the reduction of various organic functionalities using borane. The reactions utilize a fluororous borane-sulfide that overcomes the problems associated with BMS and similar borane complexes utilized in prior hydroboration and borane reduction reactions.

The present invention, therefore, is directed to readily regenerated and recycled fluororous borane-sulfides useful in hydroboration and reduction reactions. Using a virgin or a recycled fluor-

ous borane-sulfide of structural formula (I) retains all the desirable properties of the hydroboration and reduction reactions, while overcoming the problems associated with borane-BMS and other hydroborating complexes.

The fluorous borane-sulfides useful in the present invention have a structural formula (I)



(I)

wherein R_f is a fluorinated hydrocarbon chain having one to twelve carbon atoms; R is C_{1-4} alkyl or $(\text{CH}_2)_n - \text{R}_f$; and n is an integer 1 to 3.

An important feature of the fluorous borane-sulfides (I), and the present hydroboration and reduction methods, is regeneration and recycling of the fluorous borane-sulfide. The recycling process optionally includes an extraction step using a perfluorinated hydrocarbon solvent, and includes a borating step using BH_3 . Perfluorohydrocarbons, also termed fluorous hydrocarbons, are produced industrially on a large scale. They are immiscible with both common organic solvents and water. Organic chemical moieties linked to a perfluorohydrocarbon chain of sufficient size are extracted from an organic solvent into a fluorous hydrocarbon, thereby allowing their ready recovery and recycling. See A. Studer et al., *Science*, 275, pp. 823-826 (1997);

I.T. Horvath, *Acc. Chem. Res.*, 31, pp. 641-650 (1998); and D.P. Curran, *Angew. Chem. Int. Ed. Engl.*, 37, pp. 1174-1196 (1998). Fluororous compounds also can be separated from standard organic solvents
5 by preferential retention on a fluororous silica gel followed by subsequent elution with a fluororous solvent. See Q. Zhang et al., *J. Org. Chem.* 65, pp. 8866-8873 (2000).

The fluororous borane-sulfides of structural
10 formula (I) require a sufficient amount of fluorine for solubilization or dispersion in a perfluorinated solvent. In accordance with an important feature of the present invention, a fluororous borane-sulfide requires at least 35% fluorine by weight, and preferably
15 at least about 38% fluorine, by weight, of the fluororous sulfide. In general, the fluororous borane-sulfide contains at least 35% to about 70%, and preferably about 40% to about 65%, by weight of the fluororous sulfide, fluorine. To achieve the full advantage
20 of the present invention, the fluororous borane-sulfide contains about 45% to about 65%, by weight of the fluororous sulfide, fluorine.

The weight percent fluorine in the fluororous borane-sulfide is determined by the length of
25 the R_f chain or chains, and the amount of fluorine in the R_f chain or chains. If the fluororous borane-sulfide contains two R_f groups, the R_f groups can be the same or different.

Another important feature of the present
30 invention is the length of the spacer linking the fluorinated alkyl chain to the S-BH₃ moiety of the

fluorous sulfide. Fluorous-borane sulfides lacking a spacer, i.e., having a fluorinated alkyl chain bound directly to the S-R moiety (i.e., $n=0$), are unsuitable because the nucleophilicity of the fluorous sulfide is reduced, and, therefore, have a disadvantage of reduced adhesion to borane. A linker having one methylene group (i.e., $n=1$) is useful, but has a disadvantage of eliminating hydrogen fluoride (HF) from the sulfide. A linker having three methylene groups also is effective, but requires a longer R_f chain for efficient extraction in the recycling process. Therefore, fluorous borane-sulfides of structural formula (I) having two methylene group spacers (i.e., $n=2$) are preferred, and an especially preferred embodiment utilizes perfluorinated R_f chains, e.g., perfluorohexyl or perfluorooctyl, as the fluorinated alkyl chain. A perfluorooctyl group provides a fluorous borane-sulfide reagent having about 65%, by weight of the fluorous sulfide, fluorine, when R is methyl.

Preferred fluorous borane-sulfides (I) for use in the hydroboration reaction, therefore, contain one R_f group containing four to ten, and more preferably six to eight, carbon atoms. The R_f group preferably is perfluorinated. In preferred embodiments, the R group is methyl or ethyl, and n is 2.

Important features of the present invention included (a) the facile preparation of crystalline, odor-free borane-sulfides, e.g., 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptafluorodecyl methyl sulfide, and its borane complex, hereafter termed

fluororous BMS, and its higher and lower homologs, (b) their use in hydroboration and reduction reactions, and (c) their regeneration and recycling using an optional biphasic extraction with an industrial per-
5 fluorinated hydrocarbon solvent and a boration using BH_3 .

Fluororous sulfides (S. Diené et al., *J. Fluorine Chem.*, 28, pp. 425-440 (1985)) and sulfoxides have been synthesized previously using alternative, longer routes. However, a fluororous borane-sulfide, and its use in a hydroboration or reduction reaction, have not been disclosed. The present invention also is directed to an improved method of synthesizing fluororous sulfides, i.e., compounds hav-
10 ing a structure $\text{R}_f-(\text{CH}_2)_n-\text{S}-\text{R}$.^{17, 18}

After considering (i) the preference for $\geq 60\%$ fluorine by weight to facilitate regeneration and recycling of the borane-sulfide; (ii) the need for a spacer between the sulfide moiety and the
20 fluororous group to modulate the strongly electron-withdrawing ability of the fluororous group; and (iii) economic considerations, 2-(perfluorooctyl)ethyl methyl sulfide (i.e., Compound 1, 65.4% F) and its corresponding borane adduct Compound 2 (63.6% F)
25 were prepared.

In general, fluororous DMS was readily synthesized from commercial 3,3,4,4,5,5,6,6,7,7,-
8,8,9,9,10,10,10-heptafluorodecyl iodide by displacement using potassium thioacetate, followed
30 by saponification in the presence of methyl iodide. This synthetic route differs from, and is a con-

siderable improvement over prior syntheses of Compound 1 and homologs of Compound 1. Compound 1 is a colorless, odorless oil.

The passage of borane gas through neat
5 Compound 1 results in the formation of a white solid containing an approximately one-to-one mixture of Compound 1 and Compound 2. This solid mixture then is suspended in FC-72, perfluorohexane, or other
10 fluorous solvent, for use in hydroborations and other reductions. Alternatively, the fluorous suspension of Compound 2 can be generated directly by the passage of borane gas into a fluorous solution of Compound 1.

Hydroborations and reductions using Compound 2
15 are performed in biphasic mixtures containing a fluorous suspension of Compound 2 and a solution of the substrate in an appropriate organic solvent, such as dichloromethane. After the reaction is complete, the spent fluorous phase is removed,
20 and the organic phase is subjected to any necessary further treatments and workup standard in the art. For example, in the case of hydroboration, after removal of the spent fluorous solution, the organic layer containing the organoborane compounds
25 is oxidized with alkaline hydrogen peroxide to yield alcohol products. Alternatively, reactions can be conducted in a single organic phase by addition of the solid mixture of Compound 1 and Compound 2. In such instances, the spent fluorous reagent is re-
30 covered after the reaction is complete by extraction into a fluorous solvent, such as perfluorohexane.

In particular, the synthesis of Compound 1 was achieved using an improved method, in 76% overall yield, by displacement of iodide from 2-(perfluorooctyl)ethyl iodide using potassium thioacetate, followed by saponification with concomitant alkylation of the thiolate using methyl iodide (Scheme 1). The passage of borane gas, generated from $\text{BF}_3 \cdot \text{OEt}_2$ and NaBH_4 ,¹⁹ through the neat, liquid sulfide (Compound 1) resulted in the formation of a white solid that was estimated by ^1H -NMR spectroscopy to be an approximately 1:1 mixture of Compounds 1 and 2.

The ^{11}B -NMR spectrum of this mixture had a single resonance at δ -22 ppm consistent with the formation of Compound 2. Likewise, the ESI mass spectrum of the mixture demonstrated a molecular ion at m/z 509.3 in full agreement with the formation of Compound 2. Both Compound 1 and the mixture of Compounds 1 and 2 are completely odorless. The solid mixture of Compounds 1 and 2 hydrolyzed slowly on standing in air at room temperature, and additionally showed no tendency to ignite at room temperature. The mixture of Compounds 1 and 2 is stable indefinitely under a nitrogen or argon atmosphere in a refrigerator.

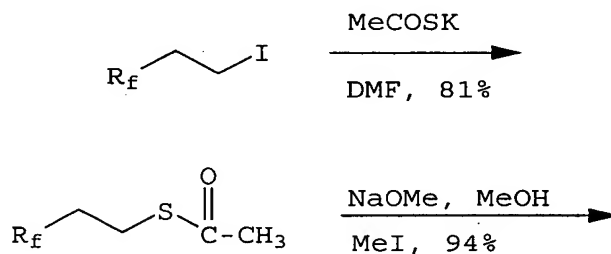
The substantial stability of the solid mixture of Compounds 1 and 2 in air enables this reagent to be weighed on a simple laboratory balance. This, coupled with the ready determination of the stoichiometry of the mixture by integration of the ^1H -NMR spectrum of the mixture, affords a simple,

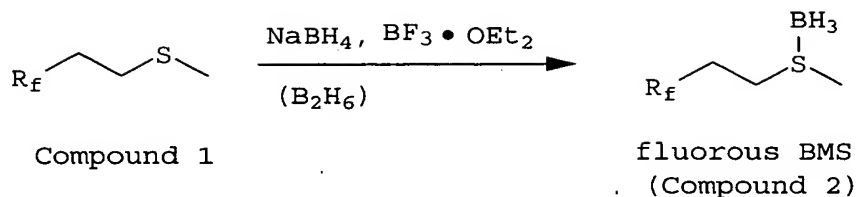
convenient method of adding precise amounts of the solid mixture to a reaction, which is in contrast to the cumbersome determination of hydrogen released during hydrolysis that typically is used to determine the amount of BMS and similar reagents to be used in a reaction.²⁰

The solid mixture of Compounds 1 and 2 contains a high fluorine content, but was only sparingly soluble in the perfluorohydrocarbon FC-72 (i.e., perfluorohexane), with which it typically forms a fine suspension. The 1:1 mixture is completely soluble in dichloromethane and benzotrifluoride²¹ (trifluoromethylbenzene). Either the solid mixture of Compounds 1 and 2, or a suspension in FC-72 or solution in a common organic solvent, can be used in the present methods.

The following reaction scheme illustrates the synthesis of a fluorous sulfide e.g., Compound 1, and a fluorous borane-sulfide complex, e.g., fluorous BMS (Compound 2, wherein $R_f = C_8F_{17}$):

Scheme 1. Preparation of a Fluorous Borane-Sulfide Complex

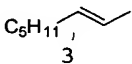
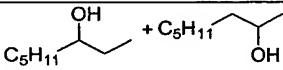

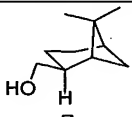

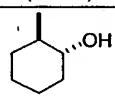
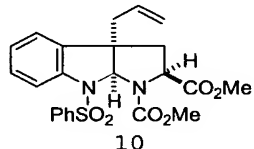
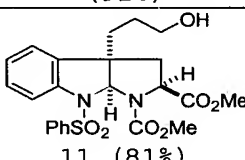
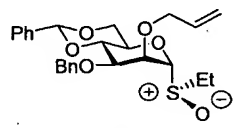
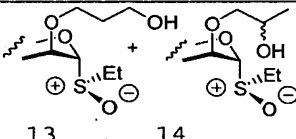




To illustrate the usefulness of a compound of structural formula (I), a series of five hydroborations were conducted using an FC-72 dispersion of the mixture of Compounds 1 and 2 (1.7 M in Compound 2). The test results are set forth in Table 1. These reactions were conducted under a nitrogen blanket in a biphasic mixture of FC-72 and dichloromethane (CH₂Cl₂). After consumption of the olefin, the spent fluorous phase was separated from the reaction mixture for recycling, and the organic phase was subjected to oxidative work up using alkaline hydrogen peroxide in a standard manner known to persons skilled in the art. The majority (i.e., about 80%) of Compounds 1 and 2, depleted in Compound 2 because of the hydroboration reaction, was recovered from the FC-72 phase. An additional 10% of Compounds 1 and 2 was recovered from the organic phase following the oxidative work-up and chromatography. Importantly, no oxidation of the sulfide Compound 1 to a sulfoxide or sulfone was observed under the oxidative work-up conditions.

The recovered Compounds 1 and 2 then were subjected to treatment with borane to regenerate additional Compound 2. The recycled Compound 2 performed exactly the same as a virgin sample of Compound 2.

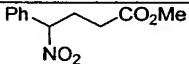
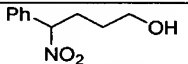
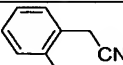
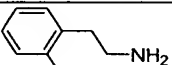
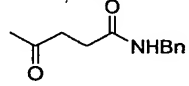
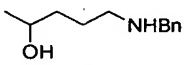
Of the five examples set forth in Table 1, the first example is a straightforward hydroboration of 2-octene, and oxidative work-up provided a mixture alcohols 4 and 5. The second example is a
5 hydroboration of β -pinene and performs exactly as expected from literature reactions using BMS⁴ and borane.²² The third example, i.e., the hydroboration of a trisubstituted alkene, proceeded in high yield and regio and stereoselectivity, as discussed in the
10 literature.²³ The fourth example shows reaction compatibility with organic functionality,²⁴ such as found in synthesis of a typical pharmaceutical. The fifth example is an unusual example of hydroboration in the presence of a sulfoxide.²⁵ The reduced regio-
15 selectivity observed in this example is typical of that seen in BMS hydroborations of other allyl ethers²⁶ and alkenes substituted with electron-withdrawing groups in general.²⁷ Compound 2, therefore, functions in hydroboration reactions exactly like
20 BMS, but with important advantages, including a reaction that is odor free, that avoids the generation of dimethyl sulfide, that can be conducted in an organic/fluorous biphasic mixture, and with straightforward regeneration and recycling of
25 Compound 2.

Table 1. Hydroboration with Fluorous BMS (2)			
Substrate	Molar equivs of Compound 2	Products (% yield)	% Recovered Compounds 1/2
 3	0.35	 4 5 (1:1.2, 90%)	92
 6	0.35	 7 (93%)	91
 8	0.35	 9 (91%)	90
 10	0.35	 11 (81%)	92
 12	0.35	 13 14 (3:1, 78%)	92

The FC-72 suspension of Compounds 1 and 2,
 5 in a biphasic manner with ready regeneration and re-
 cycling of Compound 2, also was used to perform a
 series of other reductions (Table 2). Thus, treat-
 ment of a nitroester (15) with the FC-72 dispersion
 of Compound 2 (in admixture with Compound 1) enabled
 10 reduction of the ester group without complications
 from the nitro group. This result compares to that
 previously obtained using a $\text{BH}_3 \cdot \text{THF}$ complex.²⁸ A
 nitrile (17) also was reduced to a primary amine in

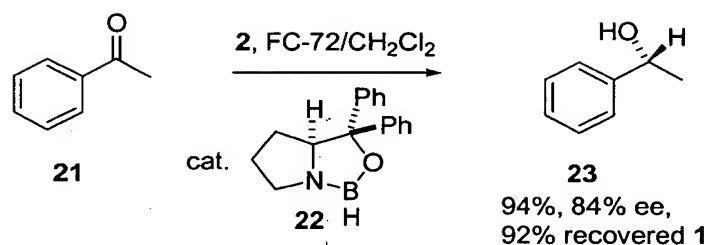
a straightforward manner, and *N*-benzyl-levulinamide (19) was converted to *N*-benzyl 4-hydroxypentylamine (20), thereby demonstrating the ability of fluorous BMS to reduce both amides and ketones.⁶

5

Table 2. Further Reductions with Fluorous BMS (2)			
Substrate	Molar equivs of Compound 2	Products (% yield)	% Recovered Compounds 1/2
 15	1.2	 16 (83%)	95
 17	1.2	 18 (81%)	88
 19	3	 20 (79%)	86

Finally, the ability of Compound 2 to re-
generate Corey-type oxaborolidine catalysts²⁹ in an
asymmetric reduction was investigated (Scheme 2).
In this reaction, reduction of acetophenone in
tetrahydrofuran (THF) using an FC-72 dispersion of
Compounds 1 and 2 catalyzed by 10 mol% of catalyst
22 resulted in the formation of (γ)-1-hydroxyethyl-
benzene in 94% yield and 84% ee, as determined by
chromatography over a Chircel OD column.

Scheme 2



In summary, FC-72 dispersions of Compound 1 and 2 perform in a manner analogous to BMS itself. However, fluoroborane-sulfides of the present reaction provide several important advantages over BMS and similar borane complexes. First, Compound 2 and similar fluoroborane-sulfides, and its reduction product Compound 1, are completely odorless. Second the spent FC-72 dispersion, enriched in Compound 1, is readily regenerated by the passage of borane gas to provide regenerated Compound 2. Third, both the solid mixture of Compounds 1 and 2, and its suspension in FC-72, are stable under a nitrogen atmosphere, and show no tendency to ignite in air. Finally, the solid mixture of Compounds 1 and 2 can be readily weighed in air and the reaction stoichiometry determined by standard ¹H-NMR spectroscopy, thereby permitting facile calculation and use of precise quantities of borane in the reaction. These improvements illustrate that suspensions of Compounds 1 and 2, and similar fluoroborane-sulfide complexes, used as a solid, suspended in a fluorocarbon solvent, or used as a solution in a standard organic solvent are suitable for large scale indus-

trial hydroborations and reductions with simple regeneration at a remote borane generation facility.

In particular, given the unstable nature of borane itself, a system is readily envisioned wherein a facility skilled in the art of generating and handling borane generates safe, nonflammable fluororous suspensions of a fluororous borane-sulfide of structural formula (I), then ships the fluororous borane-sulfide to a hydroboration or reduction production facility. After use in a two-phase reactor for example, the spent fluororous solution is returned to the borane facility for regeneration. A further advantage of the solid mixture of Compound 1 and Compound 2 is the ability to weigh the mixture in air, then determine the exact amount of available borane by simple integration of the ^1H NMR spectrum. Typically, boranes are analyzed by a cumbersome procedure involving controlled hydrolysis under an inert atmosphere with determination of the volume of hydrogen gas released.

As illustrated in Tables 1 and 2, reactions utilizing a fluororous borane-sulfide of the present invention retain the mild conditions and scope of a classic hydroboration reaction in the presence of a wide range of functional groups. The properties that lead to the popularity of the classic hydroboration reaction, therefore, have been retained. In addition to the classic hydroboration of alkenes and alkynes, Tables 1 and 2 show that a reaction using a fluororous borane-sulfide complex is compatible with various functional groups.

An important additional feature of the present invention is recovery of the fluororous sulfide in a high yield, followed by boration to regenerate a fluororous borane-sulfide of structural formula (I).

Fluorinated solvents useful in the hydroboration and reduction reactions in conjunction with the fluororous borane-sulfides of the present invention include, but are not limited to, aliphatic perfluorocarbons containing five to ten carbon atoms and perfluorinated cycloalkanes containing six to ten carbon atoms. Specific examples of fluorinated solvents include, but are not limited to, perfluorohexane, perfluoroheptane, perfluorooctane, perfluorononane, perfluorocyclohexane, perfluoromethylcyclohexane, perfluoro-1,2-dimethylcyclohexane, perfluoro-1,3-dimethylcyclohexane, cis-perfluorodecalin, trans-perfluorodecalin, perfluorokerosene, perfluoromethyldecalin, FC-72, and mixtures thereof.

After recovery of the fluororous sulfide and spent fluororous borane-sulfide, and boration of the recovered material to a fluororous borane-sulfide (I), the recycled fluororous borane-sulfide (I) performed analogously to freshly synthesized fluororous borane-sulfide (I). In fact, a fluororous borane-sulfide (I) was routinely recycled with no attempt to discriminate from virgin material.

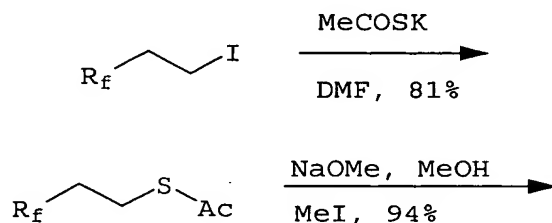
The following examples illustrate an efficient method of preparing and using a fluororous borane-sulfide of structural formula (I) in a hydroboration or a reduction reaction. A wide range of

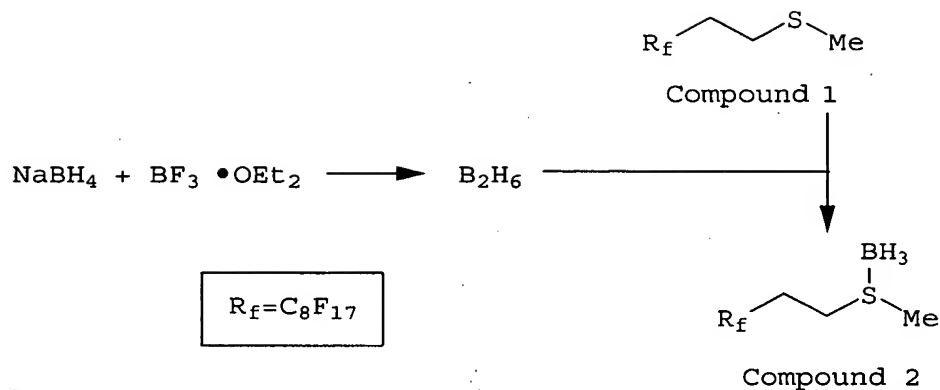
alkenes and alkynes can be hydroborated, then oxidized to yield alcohols, in high yield, under completely odor-free reactions. A compound of structural formula (I) also can be used in a variety of reactions to reduce organic functional groups. The
5 fluorous borane-sulfide (I) then is recovered, and regenerated for reuse by a simple boration using BH_3 .

Experimental Procedures

General

10 All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Methylene chloride was
15 distilled from calcium hydride prior to use. ^1H , ^{13}C and ^{19}F NMR spectra were recorded in deuteriochloroform solutions at 500 or 300, 125 or 75, and 282 MHz, respectively. All reactions were performed under a dry nitrogen or argon atmosphere unless
20 otherwise indicated. All hydroboration substrates either were commercially available or prepared as described in the literature. With the exception of Compounds 11, 13, and 14, all hydroboration products were identical to either commercial or literature
25 samples.





***S*-[2-(Perfluorooctyl)ethyl] Thioacetate**

5 To a stirred solution of potassium thioacetate (MeCOSK) (1.0 g, 8.75 mmol) in dimethylformamide (DMF) (100 mL) under an argon (Ar) blanket was added pefluorooctylethyl iodide (5.0 g, 8.70 mmol). The resulting mixture was stirred at room tempera-

10 ture for 2 hours. The reaction mixture then was taken up in ether (100 mL) and washed with saturated ammonium chloride (NH₄Cl) (30 mL), brine (30 mL), and water (50 mL). Concentration of the organic layer, followed by silica gel chromatography (hexanes:ethyl

15 acetate (EtOAc) 10:1) provided the known thioacetate¹ (3.7 g, 81%) as a very pale yellow oil. ¹H NMR δ: 3.11-3.06 (m, 2H), 2.47-2.29 (m, 2H), 2.36 (s, 3H).

3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptafluorodecyl Methyl Sulfide (1)

20 To the above fluorous thioacetate (3.25 g, 6.20 mmol), dissolved in methanol (MeOH) (40 mL) and cooled to 0°C under an inert atmosphere, was added a

freshly prepared solution of sodium methoxide (NaOMe) (0.33g, 14.95 mmol) in MeOH (6.3 mL) dropwise. The reaction mixture then was stirred for 0.5 hours before methyl iodide (MeI) (2.1 g, 14.8 mmol) dissolved in MeOH (5 mL) was added dropwise over a period of 10 minutes at 0°C. After stirring at room temperature for one hour the reaction mixture was poured into cold water and extracted with ether. Concentration of the ether layer followed by silica gel chromatography (hexanes:EtOAc 40:1) yielded the fluororous sulfide Compound 1 (2.9 g, 94%) as a colorless oil. ^1H NMR δ : 2.74-2.69 (m, 2H), 2.47-2.33 (m, 2H), 2.16 (s, 3H). ^{13}C NMR δ : 120.2-104.6 (m), 31.8 (t), 24.8 (t), 15.5 (s). ^{19}F NMR δ : -8.3 (t), -41.9 (t), -49.3, -49.4, -49.5, -50.3, -51.0, -3.7. ESIMS Calcd. For $\text{C}_{11}\text{H}_7\text{F}_{17}\text{S}$ $[\text{M}-\text{H}]^+ : 493.1$. Found 493.1.

**Solid Mixture of Fluororous Sulfide (1)
and Fluororous Borane-Sulfide (2)**

Diborane gas (B_2H_6), generated by reacting sodium borohydride (NaBH_4) (1.5 g, 39.0 mmol) in diglyme (12 mL) with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (6 mL) was passed through the neat fluororous sulfide (1) (2.9 g, 5.88 mmol) at 25°C for a period of 10 minutes, after which the oily fluororous sulfide was converted into a white solid. ^1H NMR spectroscopy showed a 1:1 relation of Compounds 2:1 (coordinated:noncoordinated) and ^{11}B NMR showed a single resonance at -22.0 ppm corresponding to Compound 2. ESIMS Calcd. For $\text{C}_{11}\text{H}_{10}\text{BF}_{17}\text{S}$ $[\text{M}+\text{H}]^+ : 509.0$. Found 509.3. An ^1H NMR spectrum of the mixture showed the above resonances

for Compound 1 and the following resonances for
Compound 2: δ 2.89-2.83 (m, 1H), 2.77-2.71 (m,
1H), 2.62 (m, 2H), 2.35 (s, 3H).

**Typical Procedure for the Hydroboration of
5 Alkenes with the Mixture of Compounds 1 and 2**

To alkene 12 of Table 1 (0.15 g, 0.32 mmol) dissolved in a biphasic solvent system of methylene chloride (CH_2Cl_2) (2 mL) and FC-72 (2 mL) under argon was added the 1/1 mixture of Compounds 1
10 and 2 (0.1 g, 0.1 mmol of Compound 2) at 0°C, followed by stirring for one hour. The FC-72 layer then was removed, and the organic layer oxidized by adding 3 M sodium hydroxide (NaOH) (0.035 mL, 0.105 mmol) and 30% hydrogen peroxide (H_2O_2) (0.019 mL,
15 0.165 mmol), followed by stirring overnight. Evaporation of the FC-72 phase provided Compound 1 (0.08 g, 80%). The CH_2Cl_2 layer was diluted with water (2 mL), and stirred for 0.5 hour. Evaporation of the CH_2Cl_2 , followed by column chromatography (hexanes:-
20 EtOAc 40:1-3:1) gave the fluorous sulfide Compound 1 (0.01 g, 10%), followed by the alcohols 13 (0.087g, 59%) and 14 (0.029g, 19%) of Table 1 in a 3:1 ratio. Alcohol 13: ^1H NMR δ : 7.50-7.26 (m, 10H), 5.62 (s, 1H), 4.89 (d, J = 11.7 Hz, 1H), 4.75 (d, J = 11.7
25 Hz, 1H), 4.61 (d, J = 1.2 Hz, 1H), 4.33 (dd, J = 3.6, 1.2 Hz, 1H), 4.25-4.16 (m, 2H), 4.09 (dd, J = 9.7, 3.6 Hz, 1H), 3.93-3.88 (m, 1H), 3.83-3.66 (m, 5H), 3.01-2.94 (m, 1H), 2.74-2.67 (m, 1H), 2.60 (br.s, 1H), 1.84-1.80 (m, 2H), 1.39 (t, J = 7.5 Hz,
30 3H); ^{13}C NMR δ : 137.7, 137.2, 129.2, 128.6, 128.4,

128.2, 128.1, 126.1, 101.8, 92.5, 78.2, 75.8, 74.4,
73.9, 71.0, 70.1, 68.2, 60.9, 44.1, 32.2, 6.1.

Alcohol 14 ¹H NMR (14) δ: 7.48-7.26 (m,
10H), 5.63 (s, 1H), 4.89 (dd, *J* = 11.55, 5.1 Hz,
5 1H), 4.77 (d, *J* = 12 Hz, 1H), 4.58 (s, 1H), 4.41-
3.99 (m, 5 H), 3.84-3.57 (m, 3 H), 3.47-3.29 (m,
1H), 2.99-2.94 (m, 1H), 2.74-2.67 (m, 1H), 1.40 (t,
J = 7.5 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H); ¹³C NMR δ:
137.5, 137.1, 129.3, 128.6, 128.4, 128.2, 128.1,
10 126.1, 101.8, 92.6, 78.9, 78.3, 76.3, 75.3, 73.9,
70.0, 68.2, 67.2, 64.7, 44.2, 18.2, 6.0.

**(+)-(2*S*,3*aR*,8*aS*)-3*a*-(3-Hydroxypropyl)-1,2-bismeth-
oxycarbonyl-8-phenylsulfonyl-1,2,3,3*a*,8,8*a*-hexa-
hydropyrrolo[2,3*b*]indole**

15 Compound 11 from Table 1 was prepared
generally as alcohols 13 and 14. ¹H NMR δ: (50°C)
7.97 (d, *J* = 6.9, 3.9 Hz, 2H), 7.55-7.46 (m, 3H),
7.30 (d, *J* = 8.1 Hz, 1H), 7.26-7.19 (m, 1H), 7.08-
7.04 (m, 2H), 6.06 (s, 1H), 4.64 (d, *J* = 9.0 Hz,
20 1H), 3.49 (t, *J* = 6.0 Hz, 2H), 3.35 (br.s, 3H), 3.18
(s, 3H), 2.68 (d, *J* = 12.9 Hz, 1H), 2.35 (dd, *J* =
12.9, 9.3 Hz, 1H), 1.68-1.58 (m, 3H), 1.43 (br.s,
1H), 1.41-1.36 (m, 1H); ¹³C NMR δ: 171.2, 154.6,
142.8, 134.2, 132.7, 129.3, 129.2, 125.7, 124.4,
25 124.1, 116.7, 83.4, 62.6, 59.8, 52.3, 52.2, 39.4,
34.8, 27.7. [α]_D = +23° (c = 1.1 g / 100 mL CHCl₃).

**Typical Procedure for the Reduction of Esters
Using the Mixture of Compounds 1 and 2**

To ester 15 of Table 2 (0.036 g, 0.162
30 mmol) dissolved in a biphasic system containing THF

(1 mL) and FC-72 (1 mL) was added the 1/1 mixture of
Compounds 1 and 2 (0.19 g, 0.19 mmol of Compound 2),
followed by stirring for 18 hours. After completion
of the reaction, MeOH (0.5 mL) was added to quench
5 excess borane. The FC-72 layer was evaporated to
provide Compound 1 (0.16 g, 84%). The organic layer
was concentrated and purified by silica gel column
chromatography (hexanes:EtOAc 40:1-3:1) to yield
Compound 1 (0.02 g, 11 %) followed by the alcohol 16
10 of Table 2 (0.03 g, 95%).

**Typical Procedure for the Reduction of Nitriles
Using the Mixture of Compounds 1 and 2**

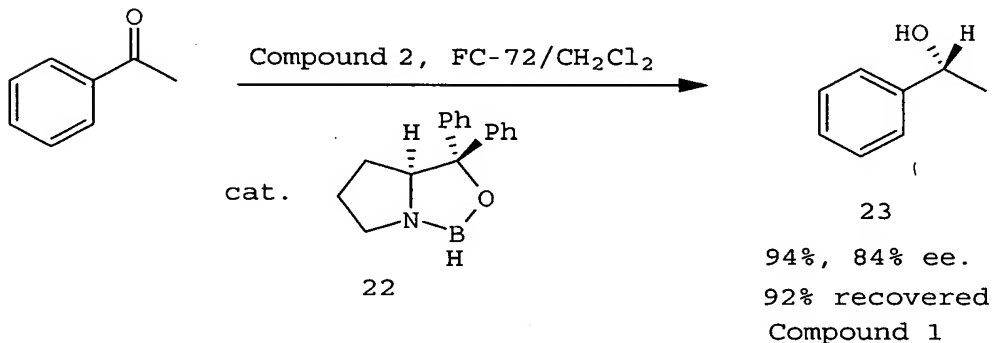
To nitrile 17 of Table 2 (0.02 g, 0.15
mmol) dissolved in THF (1 mL) was added the 1/1
15 mixture of Compounds 1 and 2 (0.18 g, 0.18 mmol of
2), followed by refluxing for 3 hours. The reaction
mixture then was cooled to room temperature, and 6 N
hydrochloric acid (HCl) (0.09 mL, 0.54 mmol) was
added dropwise. The reaction mixture then was
20 heated under reflux for 0.5 hour. The resulting
clear solution was cooled to 0°C, and FC-72 (1 mL)
was added followed by stirring for another 60 min-
utes. The FC-72 then was removed, and evaporated to
provide Compound 1 (0.13g, 78%). The organic-aque-
25 ous reaction mixture then was basified with 3 M NaOH
(0.30 mL, 0.90 mmol), and the liberated amine ex-
tracted with ether (5 mL). Concentration of the
ether layer followed by column chromatography on
silica gel (hexanes:EtOAc 40:1-25:1) yielded fluor-

ous sulfide Compound 1 (0.02 g, 10%) followed by the amine 18 of Table 2 (0.016 g, 81%).

**Typical Procedure for the Reduction of Amides
Using the Mixture of Compounds 1 and 2**

5 To amide 19 of Table 2 (0.03 g, 0.14 mmol)
dissolved in a THF (1 mL) and FC-72 (1 mL) biphasic
system was added the 1/1 mixture of Compounds 1 and
2 (0.42 g, 0.42 mmol of 2), followed by refluxing
for 4 hours. The reaction mixture then was cooled,
10 and the FC-72 layer evaporated to yield Compound 1
(0.33 g, 78%). Methanol (0.5 mL) was added to the
organic layer, which then was refluxed for 0.5 hour.
The organic layer then was concentrated, and puri-
fied by flash column chromatography on silica gel
15 (hexanes:EtOAc 40:1→1:20) to yield the fluorous
sulfide Compound 1 (0.03 g, 8%) followed by amine 20
of Table 2 (0.021 g, 79%).

**Typical Procedure for the Oxaborolidine
Catalyzed Reduction of Ketones with the
20 Mixture of Compounds 1 and 2**



To Compound 22 (0.004 g, 0.0150 mmol) dissolved in a biphasic system containing THF (0.5 mL) and FC-72 (0.5 mL) was added the 1/1 mixture of Compounds 1 and 2 (0.30 g, 0.30 mmol of 2), followed by stirring at 45°C overnight. Acetophenone (0.018 g, 0.150 mmol) then was added dropwise over a period of 30 minutes. After stirring for an additional 30 minutes, the reaction mixture was quenched with MeOH (0.3 mL). The FC-72 layer was separated from the reaction mixture, and the organic layer then was stirred with additional FC-72 (1 mL). The FC-72 layers were combined and concentrated to provide Compound 1 (0.24 g, 80%). The organic layer was concentrated and purified by column chromatography on silica gel (hexanes:EtOAc 40:1-1:20) to provide fluorosulfide Compound 1 (0.04 g, 12%) followed by (R)-(+)-1-phenylethanol (23) (0.017g, 94%). $[\alpha]_D = +40^\circ$ (c = 0.4g / 100 mL CH₂Cl₂), 84% ee. See C. Naud et al., *Fluorine Chem.*, 104, pp. 173-184 (2000).

The present invention, therefore, is directed to an efficient method of preparing fluorosulfides and their boration to the corresponding fluorosulfide borane-sulfides. The fluorosulfide borane-sulfides hydroborate a variety of alkenes and alkynes, and reduce a variety of organic functional groups, to provide desired products in excellent yield. Undesired products are avoided by use of the fluorosulfide borane-sulfides of structural formula (I), and noxious by-products are not generated. The fluorosulfide

sulfide is efficiently recovered for reuse by a simple extraction and evaporation of the fluorinated solvent, followed by boration to regenerate the fluororous borane-sulfide for recycling. The entire
5 hydroboration and reduction processes are odor free and suitable for industrial scale oxidations.

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Obviously, many modifications and variations of the invention as hereinbefore set forth can
5 be made without departing from the spirit and scope
thereof, and, therefore, only such limitations
should be imposed as are indicated by the appended
claims.